AD_____

Award Number: DAMD17-99-1-9379

TITLE: Improving detection of axillary lymph nodes by computer-aided kinetic feature identification in positron emission tomography

PRINCIPAL INVESTIGATOR: Xiaoli Yu, Ph.D.

CONTRACTING ORGANIZATION: The University of Southern California
Los Angeles, California 90089-9074

REPORT DATE: August 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 074-0188*



| 1. AGENCY USE ONLY (Leave blank) | 2. REPORT DATE | 3. REPORT TYPE AND DATES COVERED |
|---|---|---|
| | August 2002 | Annual (1 Aug 2001 - 31 Jul 2002) |

**4. TITLE AND SUBTITLE**

Improving detection of axillary lymph nodes by computer-aided kinetic feature identification in positron emission tomography

**5. FUNDING NUMBER**
DAMD17-99-1-9379

**6. AUTHOR(S)**

Xiaoli Yu, Ph.D.

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

The University of Southern California
Los Angeles, California 90089-9074
email xiyu@milly.usc.edu

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSORING / MONITORING AGENCY REPORT NUMBER**

**11. SUPPLEMENTARY NOTES**

**12a. DISTRIBUTION / AVAILABILITY STATEMENT**
Approved for Public Release; Distribution Unlimited

**12b. DISTRIBUTION CODE**

**13. ABSTRACT** *(Maximum 200 Words)*

The goal of this project is to improve detection of metastatic axillary breast cancer through sophisticated physiological modeling and statistical signal processing techniques. The major focus of Year 3 was to improved the feature extraction in visible, primary tumors by adding the factor analysis to the conventional ROI averaging method and to develop the optimal feature-guided filtering criteria for metastasis screening, which were applied to suppress the interference-plus-noise in dynamic data proceeding to the hypothesis test detection. Two types of filters were derived with/without using the physiological features extracted from normal tissues. A real liver phantom, filled with dual tracers, $^{11}C$ and $^{18}F$, was dynamically scanned. Three artificial lesions of different sizes were placed in the liver phantom with different lesion-to-background ratios. The performance of the modified feature extraction in the known tissues and the filtering algorithms searching for the unknowns were assessed with the phantom data. The results of phantom study demonstrated that the accuracy of feature extraction in the modified method can be dramatically improved compared to the conventional ROI analysis and that the feature-guided space-temporal filters can enhance the SNR in invisible lesion and make it become detectable. The assessment of non-invasive blood time activity extraction was also performed with patient data selected from our clinical database. all findings in theory and simulations will be continued in the extended Year 4 when more clinical data will be available.

**14. SUBJECT TERMS**
Breast Cancer, axillary disease, PET, statistical signal processing

**15. NUMBER OF PAGES**
11

**16. PRICE CODE**

| 17. SECURITY CLASSIFICATION OF REPORT | 18. SECURITY CLASSIFICATION OF THIS PAGE | 19. SECURITY CLASSIFICATION OF ABSTRACT | 20. LIMITATION OF ABSTRACT |
|---|---|---|---|
| Unclassified | Unclassified | Unclassified | Unlimited |

## Table of Contents

## 1. Introduction

Despite significant advances in primary and metastatic lesion detection with static PET, the ability to accurately detect metastases at an early stage remains the greatest challenge in oncology imaging. At an early stage, radiotracer uptake of metastatic tissue is often weak, due to the relatively fewer cells involved with disease. Moreover, the diseased tissue and abnormal uptake is, in most circumstances, embedded in severe background interference and count noise, thus hardly differentiated from surrounding normal tissues with visual inspection in either 2-D or 3-D static PET images. We have been seeking a clinically practical way to assist conventional visual inspection of static PET images with temporal information derived from a dynamic PET-FDG imaging sequence. Modeling, extracting and exploiting physiological features that can distinguish normal breast tissues from axillary malignances in dynamic PET has been pursued since the last reporting period. The study conducted in the current year was built on the previous year's research, which concentrated on the development and testing of optimal computer-aided detection criteria for kinetic feature identification from equivocal axillary metastases in noisy images. Rather than replace conventional visual image inspection, our goal is to design an intelligent system that will supplement it.

The whole proposed study consists of four tasks: *Task 1*: Developing the mathematical formula to linearly map and identify the physiological features contained in PET dynamic sinogram sequence (Month 1-8), *Task 2*: Developing the schemes for objective reduction of dynamic sinogram data guided by the identified TAC subspaces of the desired signal (tumor) and the interference (normal tissue background plus noise) (Month 4 - 12), *Task 3*: Deriving and analyzing statistical hypothesis test criteria to test the presence of an axillary metastasis in the dynamic images reconstructed from the compressed sinogram data (Month 13 - 24), and *Task 4*: Clinical Evaluation (Month 13 - 36). For each task, several subtasks were defined (see the SOW in the grant application for details).

## 2. Body

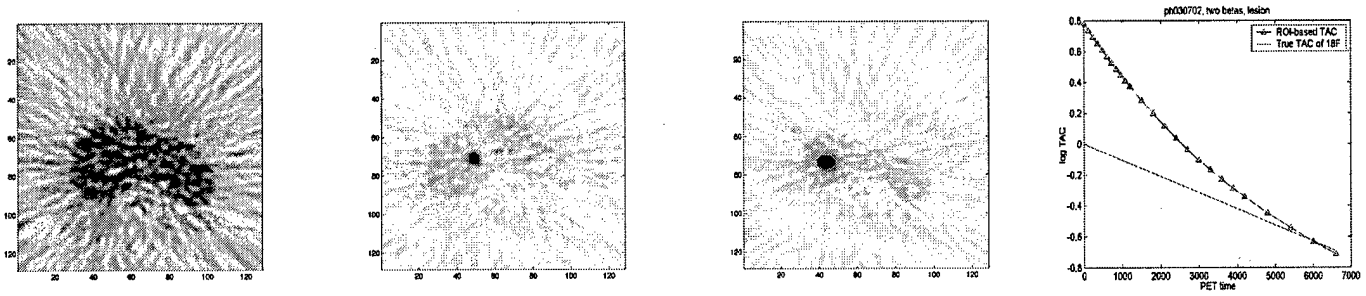
During this annual reporting period, our efforts were mainly focused on Task 4 as originally proposed for the third year of the study. However, after the first year's annual report, it was brought to our attention that we needed to obtain approval from the U.S. Army Medical Research and Material Command Institutional Review Board (US Army IRB). Although patients whose data are used in this study will have a PET scan regardless of their participation in this study, they still must be prospectively recruited for "additional" (temporal-based) images. Efforts have been made for last 1.5 years to complete the respective IRB approvals with protocol/language acceptable to USC's Institutional Review Board and the US Army IRB. Because IRB approval is pending, no clinical dynamic imaging data have been acquired nor any subjects recruited for the extra pictures since that time. Efforts in support of Task 4 have been limited to analyses of dynamic imaging data that already existed in the patient database of USC PET center as well as phantom data. Further work on Tasks 1,2 and 3 has also been continued through this year. The major accomplishments of this activity are presented as follows:

### 2.1 Assessment of accuracy of ROI-based molecular feature extraction

Using dynamic phantom data with known ground truth, we tested, to a certain degree, how the time activity curve in a large, visible lesion could be possibly interfered by its surrounding background activity through the currently used, imperfect reconstruction techniques, or lack of adequate resolution

and how the accuracy of lesion feature related parameters might be affected by the common ROI-averaged time activity curve.

**Experimental phantom study:**
We have performed an experimental study with a realistic liver phantom. In the liver phantom *three* artificial spherical lesions of different sizes and contrasts were placed inserted into the. Two tracers, $^{11}C$ and $^{18}F$, were filled into the liver and lesions, respectively, with uniform activity distributions. Dynamic data were acquired of the phantom with ECAT953 2-D whole body scanner. This allowed the radioactive decay signature of the two radiopharmaceuticals to be measured as pseudo-washout data. In the filtered backprojection reconstructed images, the smallest lesion with 7mm interior diameters was invisible in all dynamic frames, while the two largest lesions can be clearly visualized in the FBP images, see Figure 1 (a) – (d) for an illustration.




(a) (b) (c) (d)

Figure 1: (a) –(c) The last frame FBP images of the smallest, median, and largest lesions in the liver phantom; (d) The time activity curves in semi-log scale: true mono-exponential function of $^{18}F$ (red) and ROI averaged observation.

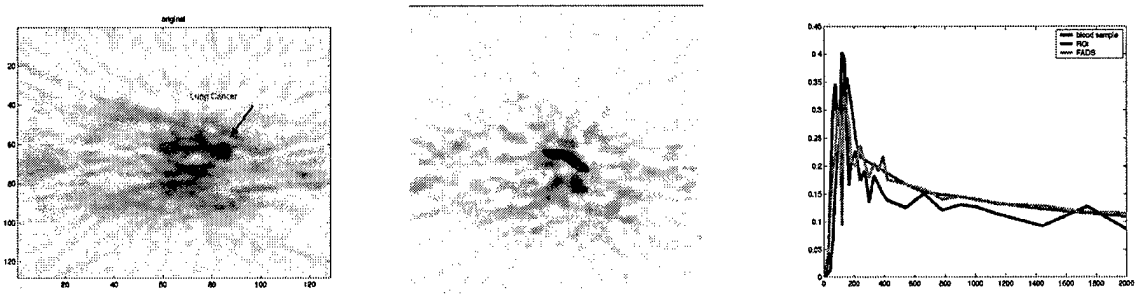
The largest lesion was used to mimic a primary tumor detected in a patient. A ROI was placed in it indicated in red in Figure 1 (c). The time activity curve in the lesion was estimated by fitting an ROI averaged observation. The resulting curve is plotted in semi-log scale and shown in Figure 1 (d). As we can see that the estimated curve in blue is far from the true $^{18}F$ time activity curve. The true curve should be a mono-exponential function and a straight line in semi-log scale. Evidently, the estimated features in lesion were severely contaminated by the activities of $^{11}C$ in the liver background. These features can not adequately characterize lesions. If we use these inaccurate lesion features to guide a filter design, then at an attempt to protect the lesion features during the filtering, we also vulnerably keep the unwanted background interference. This will definitely affect the performance of filtering and lower the SNR gain in the filtered images.

## 2.2 Assessment of non-invasive blood input function extraction

Blood input function is required in molecular feature extraction with FDG PET time activity models. We have also assessed the feasibility of replacing invasive blood sampling with non-invasive blood time activity curve extracted from dynamic image data. The most common way to get blood function is invasive blood drawing; however, operationally it is complicated, time consuming, and difficult for patients to have arterial blood draws throughout the procedure. A critical issue with the non-invasive approaches is their "ACCURACY". This is because, besides noise interference, surrounding tissues.

There are two non-invasive approaches available: one is a simple ROI based analysis and the other is the more complex FADS, or factor analysis of dynamic structure method. FADS is well known for its capability to separate time activity curves from the mixed observations.

**Patient study:** Ten lung cancer and inflammation patient data were collected for the study. The blood samples were invasively collected from all these patients. These blood samples served as gold standard in the evaluation.




(a) (b) (c)

Figure 2: (a) The last frame FBP image of a lung cancer patient; (b) The ROI used to non-invasively extract arterial blood function; (c) The three blood functions: invasive blood samples (red), FADS estimation (green) and ROI-average (blue).

This preliminary study over 10 patients concludes that when compared to invasively collected blood samples, the blood functions estimated from FDAS have the mean square errors about 7 times lower than those of ROI average method. FADS approach is potential to outperform ROI-based method for replacing the invasive blood sampling.

This work has been presented in SNM annual conference 2002, Los Angeles, CA, June 2002.

### 2.3 Assessment of improving SNR via spatial-temporal image processing

Can adding temporal information to spatial processing improve SNR in small, faint or invisible lesions? This is a critical question that this study attempts to answer. We conducted the preliminary studies with both the digital (computer generated) phantom and the liver experimental phantom data that we believe would shed light upon answering the question.

The above-mentioned liver phantom is used to test in gaining SNR in the smallest lesion through spatial-temporal processing. Figure 2 (a) – (c) shows the FBP reconstructed images of this lesion at Frame 1, 15 and 23 and Figure 2 (d) is the MAP reconstruction of Frame 23. This confirms that the lesion is invisible in all the frames using either the simple or advanced reconstruction methods. In other words, by exploiting only the spatial information in the data can not improve SNR high enough to make the lesion become detectable. To further increase SNR in the smallest lesion, making a use of the intrinsic, temporal information available in PET dynamic data is pursuable. We first tried to apply FADS to separate or remove the liver background activities and statistical noise superimposed onto the lesion, since we know that FADS is well credited in decomposing the mixed observation from visible structures. Via FADS we projected the dynamic images into the principle components of the images, but in none of the decomposed images the lesion is distinguishable. In Figure 2 (e), the first two principle component images are presented as an illustration. This

indicates that a direct application of FADS is not an answer to our problem, this is because when lesion components are too weak to be dominant components, the principle component based FADS would fail to separate them from the other dominate components. Figure 2 (f) is the result of the simplest primary tumor feature guided filtering. The technical details are given in Section I.D. 2. In this test data, the primary tumor features were extracted in the largest artificial lesion shown in Figure 1 (c) by a simple ROI average. Although the accuracy of ROI based feature extraction had been shown not high enough, the results of this study reveal that adding temporal information to image processing indeed has potential to increase SNR in small lesions, as long as the features in small and primary lesions are similar in certain degree.

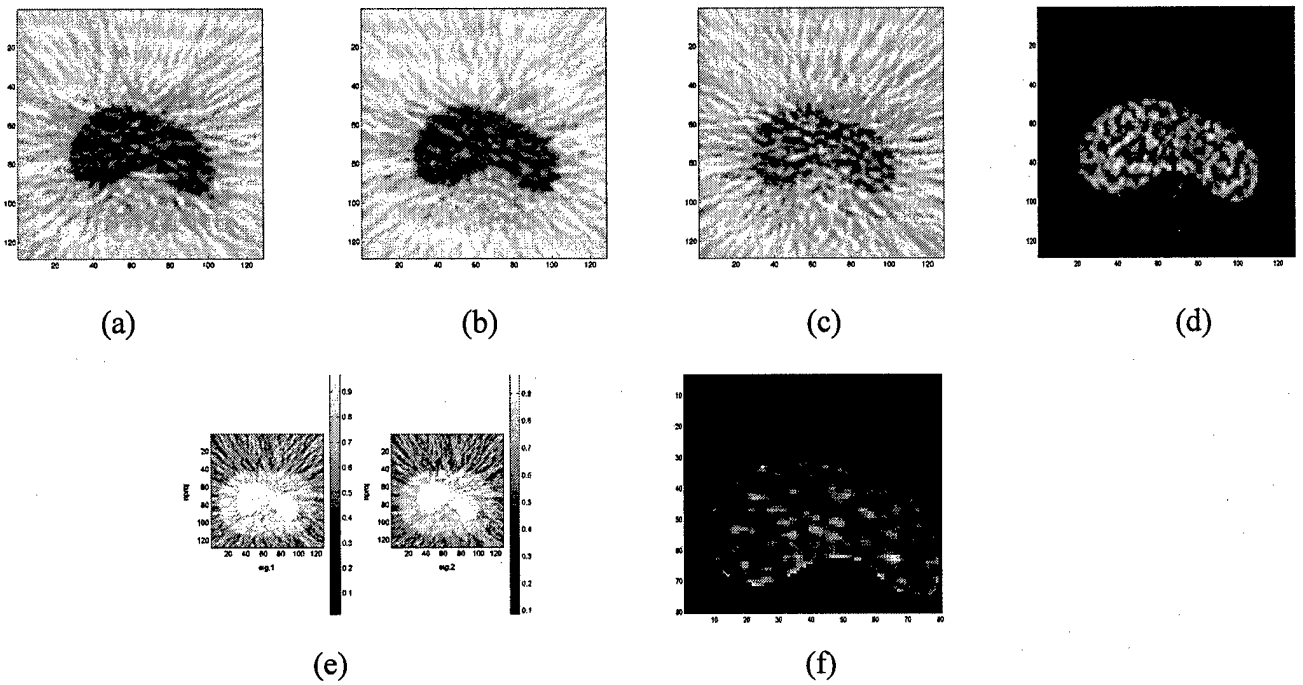


Figure 2: (a)-(c) FBP reconstruction of Frame 1,15 and 23; (b) MAP reconstruction of Frame 23; (c) FADS decomposed images; (d) filtered image using the simplest version of proposed methods.

## 2.4 Development of FADS aided ROI analysis method to improve the accuracy of feature extraction

Feature extraction in the proposal means to estimate the feature vectors, i.e., the macro-parameters from the time activity curve observations in dynamic PET images. We developed a factor analysis dynamic structure aided, or FADS-aided method against conventional ROI-average to obtain the time activity curve observations for the estimation. As we have shown in our preliminary study with the experimental liver phantom that the time activity curves obtained by simply averaging over even a suitably selected ROI in the large, high background-to-lesion contrast lesion the surrounding tissues were severely interfered by the surrounding liver background, see Figure 1 (d) in Section I.C.1. If we use the ROI average method for primary tumor feature extraction, with no doubt, the feature vectors estimated from such background interfered time activity curves must be inevitably contaminated with the background features and can not accurately characterize the tumor molecular behavior.

FADS processing is widely used in cleaning up the surrounding background time activity interferences in the blood function non-invasively extracted in dynamic images at an area with strong arterial activity. Our preliminary study found out that FADS processed blood input functions has much more fidelity to the invasively collected blood samples in patients, but, on the other hand, we have also found that FADS processing failed to remove the interferences superimposed on the invisible artificial lesions in both experimental and digital phantom studies due to low lesion-to-background ratios. Consider the detected primary tumor and the normal tissues in properly selected areas are usually strong that are analogous to the scenario of blood function extraction. Thus, we will resort to FADS processing to separate the unwanted time activities contributed from surrounding background from the observed time activities in the primary tumor and normal tissues. The feature parameters will be estimated from the FADS resulted TACs, instead from that simply averaged in ROI.

### 2.5. Development of Feature-guided filtering algorithms for metastasis identification

Time activity model of metastasis: At early stage, metastasis is small and often mixed with its surrounding background activities. We used a mixed FDG PET model in heterogeneous tissue given below to characterize its total radioactivity. Let $i$ indicate the $i^{th}$ pixel in dynamic images, then a vector form is expressed by

$$\mathbf{c}_i = \sum_{k=1}^{K} \mathbf{f}^{(k)} d_i^{(k)} + v_i^* \mathbf{c}_p^* + \mathbf{n}_i = \mathbf{F}^{(les)} \mathbf{d}_i^{(les)} + \mathbf{F}^{(tis)} \mathbf{d}_i^{(tis)} + v_i^* \mathbf{c}_p^* + \mathbf{n}_i$$

with $\mathbf{f}^{(k)}$ indicating a vector which consists of a collection of samples of $c_p^* \otimes e^{-\beta_k t}$ at time instances $t = t_1, t_2, ..., t_N$ when dynamic frames are acquired. Unless mentioned otherwise, a bold face lower case and upper case denote a vector and matrix, respectively. The notation $\mathbf{n}_i$ represents statistical noise. $\mathbf{F}^{(les)}$ and $\mathbf{F}^{(tis)}$ consist of a group of $\mathbf{f}^{(k)}$ related to tumor and normal tissue feature vectors.

No doubt in above equation the physiological vectors $\mathbf{f}^{(k)}$ and coefficient $d_i^{(k)}$ bear the tissue kinetic information. In the existing parametric image approaches, one attempts to estimate all of them simultaneously. The inherent problems with the approaches are that in most equivocal or non-palpable metastases the physiological features of normal tissues are often dominating. They will certainly lead the parameter estimation pursued by curve fitting and results in inaccuracy for estimating the weaker tumor-like features and the corresponding coefficients. A consequence of such inaccurately estimated tumor-related parameters would result in an incorrect inference to a presence of metastasis. Moreover, most of parametric image methods involve iterative optimization procedures that often make the parameter estimation a high computational complexity and divergence also frequently occurs. Therefore, we propose the following filtering approaches to mitigate these difficulties inherent to the parameter estimation for detecting heterogeneous metastatic lesions.

Given a primary tumor is present in the imaging field. Re-examining above TAC model tells us only the physiological factor matrix $\mathbf{F}^{(les)}$ and its corresponding coefficient vector $\mathbf{b}^{(les)}$ are lesion information-bearing. All other terms in the equation are interferences. When the interference is dominant, the characteristics of lesion embedded in severe interference become equivocal and not identifiable by visual inspection. We attempt to design a filter $\mathbf{w}$ to suppress the inferences from the vector of measurements, $\mathbf{c}_i$, for all pixel $i = 1,2,..,I$. Denote the processed data vector by $y_i = \mathbf{w}^T \mathbf{c}_i$, where superscript T indicates a transpose operation in linear algebra. It is our desire that the filter $\mathbf{w}$ can

remove the interferences and noise from observed TAC, $\mathbf{c}_i$, and to also protect the characterizations of lesion from being distorted by the filtering process. The following two filtering criteria and associated algorithms developed in this study.

**Tumor + normal tissue feature-guided filtering:** We designed a filter $\mathbf{W}$ to satisfy the following constraints:

$$\mathbf{W}^T\mathbf{F}^{(les)} = \mathbf{I},\ \mathbf{W}^T\mathbf{F}^{(tis)} = \mathbf{0},\ \textit{and}\ \ \mathbf{W}^T\mathbf{c}_p^* = \mathbf{0} \qquad (2)$$

where $\mathbf{I}$ denote an identity matrix. From Eqs 3 and 4 one can immediately see that the first constraint will protect the physiological features from being degraded when applying such constrained filter $\mathbf{W}$ to the vector measurements of $\mathbf{c}_i$, while the other constraints ensure a complete elimination of interference in the filtered data $\mathbf{y}_i = \mathbf{W}^T\mathbf{c}_i$, for $i = 1,2,..,I$, namely $\mathbf{y}_i = \mathbf{W}^T\mathbf{c}_i = \mathbf{d}_i^{(les)} + \tilde{\mathbf{n}}_i$, where $\tilde{\mathbf{n}}_i = \mathbf{W}^T\mathbf{n}_i$ denotes the filtered noise.

The mathematical expression of the filter $\mathbf{W}$ in a general form and the associated filtering algorithms have been derived during this project. Notice that no special attentions are given to the statistical noise $\mathbf{n}_i$ in Eq. (2). The expense is that the filter may only be suitable for processing low statistical noise images, e.g. the images reconstructed by ordered subset expectation maximization (OSEM) algorithm or maximum a posterior probability (MAP) algorithm.

**Tumor feature-guided filtering:** We also developed another filtering criterion that takes into account interference and statistical noise simultaneously. The filter minimizes the filtering output energy under a constraint that ensures the energy contributed from lesion components not being degraded. This implies that the energy of interference and noise must be minimized. Such a filtering problem can be mathematically formulated as follows

$$\mathbf{W}_{opt} = \arg\min_{w} E\left\{\left\|\mathbf{W}^T\mathbf{c}_i\right\|^2\right\},\ \textit{subject to}\ \ \mathbf{W}^T\mathbf{F}^{(les)} = \mathbf{I}, \qquad (3)$$

where notation E indicates a expectation operator and $\|\cdot\|$ denotes a norm of a vector. The above-constrained optimization problem is solvable by employing Lagrange multiplier and sophisticated linear algebraic manipulations.

There is a trade-off between the above two filtering criteria. The first completely eliminates the background tissue interference, but may worsen the statistical noise. The second takes account statistical noise, however, compromises interference suppression. We will analytically compare the performance of the two filters and quantify the signal-to-noise ratios out of the filters.

In order to use this mixture model for heterogeneous tissues, we will need a guidance of anatomic images (MRI or CT scans) to spatially partition or segment the entire dynamic PET images into several sub-regions with self-similar spatial and temporal characteristics. These anatomic images must be co-registered to the PET images.

## 3. Key Research Accomplishments

The main accomplishments in Year 3 are

1. Assessment of accuracy of ROI-based molecular feature extraction with the real liver phantom data;

2. Development of the factor analysis aided feature extraction method to improve the accuracy of feature parameter estimation;

3. Assessment of non-invasive blood input function extraction with the patient data collected in clinical database at the USC PET center;

4. Design of space-temporal filtering criteria to identify metastases embedded from the unwanted noise and background interference;

5. Assessment of improving SNR via spatial-temporal filtering algorithms with the liver phantom data;

6. Accomplishment of the respective IRB approvals with protocol/language acceptable to USC's Institutional Review Board and the US Army IRB.

## 4. List of Reportable Outcomes:

### 4.1 Publications

1. X. Yu, Z. Li, H. Jadvar and P. S. Conti, ``Assessment of Non-invasive Blood Time Activity Extraction in Dynamic PET Oncology", SNM Annual Conference 2002, Los Angeles, CA., June 2002.

2. X. Yu, C. C. Huang, and P. S. Conti, ``Computer-aided Metastasis Detection with Dynamic PET", presented at the Era of Hope Conference, Orlando, FL., September 2002.

3. X. Yu and I. S. Reed, "Theory and Algorithms of Rank Reduction for Subspace Filtering", submitted to IEEE Trans. On Information Theory, July 2002.

### 4.2 Graduation

Two students graduated with their M.S. degrees, respectively. Both were partially supported by this award.

## 5. Conclusion

The goal of this project is to improve detection of metastatic axillary breast cancer through sophisticated physiological modeling and statistical signal processing techniques. The major focus of Year 3 was to improved the feature extraction in visible, primary tumors by adding the factor analysis

to the conventional ROI averaging method and to develop the optimal feature-guided filtering criteria for metastasis screening, which were applied to suppress the interference-plus-noise in dynamic data proceeding to the hypothesis test detection. Two types of filters were derived with/without using the physiological features extracted from normal tissues. A real liver phantom, filled with dual tracers, $^{11}C$ and $^{18}F$, was dynamically scanned. Three artificial lesions of different sizes were placed in the liver phantom with different lesion-to-background ratios. The performance of the modified feature extraction in the known tissues and the filtering algorithms searching for the unknowns were assessed with the phantom data. The results of phantom study demonstrated that the accuracy of feature extraction in the modified method can be dramatically improved compared to the conventional ROI analysis and that the feature-guided space-temporal filters can enhance the SNR in invisible lesion and make it become detectable. The assessment of non-invasive blood time activity extraction was also performed with patient data selected from our clinical database. all findings in theory and simulations will be continued in the extended Year 4 when more clinical data will be available.

## 6. References


1. K. Schmidt, G. Mies, and L. Sokoloff, "Model of kinetic behavior deoxyglucose in heterogeneous tissues in brain: A reinterpretation of the significant of parameters fitted to homogeneous tissue models," J. Cerebral Blood Flow and Metabolism, Vol. 11, p. 10-24, 1991.

2. F. Osullivan, "Imaging radiotracer model parameters in PET: A mixture analysis approach", IEEE Trans. on Medical Imaging, Vol. 12, No. 3, pp. 399-412, 1993.

3. C. M. Kao, J. T. Yap, J. Mukherjee and M. N. Wernick, ``Image Reconstruction for Dynamic PET Based on Low-Order Approximation and Restoration of the Sinogram," IEEE Trans. Medical Imaging, Vol. 16, No. 6, Dec. 1997.

4. R. E. Carson, et al.,``An approximation formula for the variance of PET region-of-interest values," IEEE Trans. Med. Imag., Vol. 12, No. 2, p. 240-250, June 1993.

5. L.L. Scharf and B. Friedlander, "Matched subspace detectors", IEEE Trans. Signal Processing, Vol. 42, No. 8, p. 2146-2157, Aug. 1994.

6. R.H. Huesman, ``A new fast algorithm for the evaluation of regions of interest and statistical uncertainty in computed tomography," Phys. Med. Biol., Vol. 29, No 5, p. 543-552, 1984.

7. C. C. Huang, X. Yu, J. Bading and P. S. Conti, ``Feature extraction by subspace fitting of time activity curves in PET dynamic studies", IEEE Medical Imaging Conference, November 1997.

8. C.C. Huang, Ph.D. Thesis, submitted to USC EE department, May 2001.

9. P. Thanyasrisung, Ph.D. Thesis, submitted to USC EE department, May 2001.